



**DIGITAL ACCESS TO  
SCHOLARSHIP AT HARVARD**  
DASH.HARVARD.EDU



**HARVARD LIBRARY**  
Office for Scholarly Communication

# Response Expectancy and the Response to Antidepressant Medication

**The Harvard community has made this  
article openly available. [Please share](#) how  
this access benefits you. Your story matters**

Citation	Kirsch, Irving. 2017. "Response Expectancy and the Response to Antidepressant Medication." EBioMedicine 25 (1): 13. doi:10.1016/j.ebiom.2017.09.038. <a href="http://dx.doi.org/10.1016/j.ebiom.2017.09.038">http://dx.doi.org/10.1016/j.ebiom.2017.09.038</a> .
Published Version	<a href="https://doi.org/10.1016/j.ebiom.2017.09.038">doi:10.1016/j.ebiom.2017.09.038</a>
Citable link	<a href="http://nrs.harvard.edu/urn-3:HUL.InstRepos:34651867">http://nrs.harvard.edu/urn-3:HUL.InstRepos:34651867</a>
Terms of Use	This article was downloaded from Harvard University's DASH repository, and is made available under the terms and conditions applicable to Other Posted Material, as set forth at <a href="http://nrs.harvard.edu/urn-3:HUL.InstRepos:dash.current.terms-of-use#LAA">http://nrs.harvard.edu/urn-3:HUL.InstRepos:dash.current.terms-of-use#LAA</a>



## Commentary

## Response Expectancy and the Response to Antidepressant Medication



Irving Kirsch \*

Program in Placebo Studies, Harvard Medical School, USA

Previous studies have shown that perceived treatment assignment (placebo vs drug) is associated with response to SSRIs (e.g., [Chen et al., 2011](#)). However, interpretation of those results is hampered by the fact that they are correlational. Thus, treatment outcome may be affecting guesses about treatment assignment rather than guesses affecting outcome. The Faria et al. study in EBioMedicine is virtually unique in its use of an experimental manipulation, thereby allowing inferences of causality ([Faria et al., 2017](#)). The results are clear and compelling. Although escitalopram alleviated escitalopram even when given covertly, its effects were two to three times greater when administered knowingly. Indeed, the effect size for overt versus covert administration of this SSRI, as calculated from the data in Table 2, is very large ( $d = 1.2$ ), three times as large as the small to moderate drug-placebo effect size reported in a recent meta-analysis for the treatment of social anxiety disorder by SSRIs and SNRIs ( $d = 0.39$ ) ([Sugarman et al., 2017](#)).

These data have enormous clinical implications. They indicate that the information given to patients about SSRIs can have a greater impact than the drugs themselves. Data from other studies suggest that clinician warmth and empathy can impact both improvement and expected improvement in clinical conditions ([He et al., 2017](#); [Kaptchuk et al., 2008](#)). Taken together, these data underline the importance of training clinicians in how to communicate most effectively with patients. It is not only the specific treatment that is important in producing favorable health outcomes; it is also the clinician's ability to establish a therapeutic alliance and promote positive response expectancies.

Placebo effects and specific drug effects are components of the total response when a drug or other active treatment is given. Data and opinion are mixed on whether these effects are additive. Specifically, do non-drug aspects of treatment (e.g., knowledge that one is receiving a treatment) increase the response to the treatment. The logic of randomized clinical trials (RCTs) implies an assumption that drug and placebo effects are additive, but some writers have challenged this assumption (e.g., [Lund et al., 2014](#)). If they are not additive, they say, then conventional RCTs might underestimate the specific drug component of the treatment response.

The data from the Faria et al. study are pertinent to the issue of additivity. In particular, the size of the expectancy effect they obtained is so large that an even larger effect in placebo arms seems unlikely. Indeed, if there is a significant interaction, it may be due to the placebo effect

being larger when a real drug is given than when a placebo is given, as has been reported in a study of analgesic medication ([Schenk et al., 2014](#)). Nevertheless, the Faria et al. study was not designed to test additivity. As the authors indicate, the gold standard for assessing additivity is by use of the balanced placebo design ([Marlatt and Rohsenow, 1980](#)). The balanced placebo design comprises four arms. It is a  $2 \times 2$  design in which what participants are told (that they receive an active drug or a placebo) is crossed with what they actually receive (drug or placebo). It has been used to reveal additive and non-additive relations between drug content and expectancies with respect to responses associated with alcohol, caffeine, and analgesic medication, among other substances, but has not been evaluated with respect to antidepressant medications. The Faria et al. study contains two of the cells of the balanced placebo (told drug – get drug; told placebo – get drug). Adding the two remaining cells (told placebo – get drug; told placebo – get placebo) would be the next step in solving the puzzle of additivity.

## Disclosure

The author declared no conflicts of interest.

## References

- Chen, J.A., Papakostas, G.I., Youn, S., Baer, L., Clain, A.J., Fava, M., Mischoulon, D., 2011. Association between patient beliefs regarding assigned treatment and clinical response: reanalysis of data from the Hypericum Depression Trial Study Group. *J. Clin. Psychiatry* 72 (12), 1669–1676.
- Faria, V., Gingnell, M., Hoppe, J.M., Hjorth, O., Alaie, I., Frick, A., ... Furmark, T., 2017. Do you believe it? Verbal suggestions influence the clinical and neural effects of escitalopram in social anxiety disorder: a randomized trial. *EBioMedicine* 24, 179–188.
- He, X., Sun, Q., Stetler, C., 2017. Warm communication style strengthens expectations and increases perceived improvement. *Health Commun.* 1–7 <https://doi.org/10.1080/10410236.2017.1322482>.
- Kaptchuk, T.J., Kelley, J.M., Conboy, L.A., Davis, R.B., Kerr, C.E., Jacobson, E.E., 2008. Components of placebo effect: randomised controlled trial in patients with irritable bowel syndrome. *BMJ* 336. <https://doi.org/10.1136/bmj.39524.439618.25>.
- Lund, K., Vase, L., Petersen, G.L., Jensen, T.S., Finnerup, N.B., 2014. Randomised controlled trials may underestimate drug effects: balanced placebo trial design. *PLoS One* 9 (1): e84104. <https://doi.org/10.1371/journal.pone.0084104>.
- Marlatt, G.A., Rohsenow, D.J., 1980. Cognitive processes in alcohol use: expectancy and the balanced placebo design. In: Mello, N.K. (Ed.), *Advances in Substance Abuse: Behavioral and Biological Research*. JAI Press, Greenwich, CT, pp. 159–199.
- Schenk, L.A., Sprenger, C., Geuter, S., Büchel, C., 2014. Expectation requires treatment to boost pain relief: an fMRI study. *Pain* 155 (1):150–157. <https://doi.org/10.1016/j.pain.2013.09.024>.
- Sugarman, M.A., Kirsch, I., Huppert, J.D., 2017. Obsessive-compulsive disorder has a reduced placebo (and antidepressant) response compared to other anxiety disorders: a meta-analysis. *J. Affect. Disord.* 218 (Supplement C):217–226. <https://doi.org/10.1016/j.jad.2017.04.068>.

DOI of original article: <https://doi.org/10.1016/j.ebiom.2017.09.031>.

\* Irving Kirsch, 144 Medford Street, Arlington, MA 02474, USA.

E-mail address: [ikirsch@bidmc.harvard.edu](mailto:ikirsch@bidmc.harvard.edu) (I. Kirsch).

<https://doi.org/10.1016/j.ebiom.2017.09.038>

2352-3964/© 2017 The Author. Published by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).